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Time-Dependent Exposures and the Fixed-Cohort Bias: Hwang et al. Respond

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Barnett expresses concerns about a potential bias in our article (Hwang et al. 2011) related to use of a fixed study period based on the date of delivery: on average a shorter duration of gestation among stillbirths compared to live births in combination with seasonal variation of exposure. We acknowledge the complexity of assessing effects of exposure with seasonal variation on the risk of stillbirth and thank Barnett for his suggestion to avoid a possible bias, which he with his colleagues illustrated through simulations of a retrospective cohort study (Strand et al. 2011). We reanalyzed the data, excluding case and control subjects following Barnett's suggestion to quantify the "fixed cohort bias." This led to loss of approximately 4.7% (4,480/102,575) of the subjects. The point estimates were similar with those from the original analyses, but some confidence intervals became wider (Table 1). This shows that the role of the fixed cohort bias was minimal in our study.

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Table 1. Adjusted ORs (95% CIs) for stillbirth by average pollutant concentrations, by trimester and for the whole pregnancy (single pollutant models), following Barnett's suggestion to address the "fixed cohort bias."

Air pollutant	All births (gestational age > 20 weeks) Model 1[a]	Preterm births (gestational age < 37 weeks) Model 2[b]	Term births (gestational age ≥ 37 weeks) Model 3[b]
PM_{10} (10 μg/m^3)			
1st trimester	1.02 (0.99–1.05)*	1.03 (1.00–1.07)	1.00 (0.96–1.04)
2nd trimester	0.97 (0.94–0.99)*	0.99 (0.95–1.03)*	0.95 (0.92–0.99)*
3rd trimester	0.97 (0.95–1.00)*	0.97 (0.92–1.02)	0.97 (0.92–1.02)*
Whole pregnancy	0.97 (0.95–1.02)*	1.01 (0.96–1.06)*	0.96 (0.91–1.01)*
SO_2 (1 ppb)			
1st trimester	1.02 (1.00–1.04)	1.04 (1.01–1.06)*	1.00 (0.97–1.03)*
2nd trimester	1.00 (0.98–1.02)	1.02 (0.99–1.04)*	0.99 (0.96–1.02)
3rd trimester	1.00 (0.98–1.02)	1.01 (0.97–1.04)	1.01 (0.97–1.04)*
Whole pregnancy	1.01 (0.99–1.03)	1.03 (1.00–1.06)	0.99 (0.97–1.02)*
NO_2 (10 ppb)			
1st trimester	1.01 (0.96–1.07)	1.05 (0.97–1.13)*	0.98 (0.90–1.06)
2nd trimester	0.97 (0.92–1.02)*	1.00 (0.93–1.08)*	0.95 (0.88–1.02)
3rd trimester	0.98 (0.92–1.04)	0.98 (0.89–1.08)	0.98 (0.89–1.08)*
Whole pregnancy	0.98 (0.93–1.05)*	1.02 (0.94–1.11)*	0.96 (0.88–1.05)
CO (100 ppb)			
1st trimester	1.00 (0.98–1.02)	1.00 (0.97–1.02)*	1.01 (0.98–1.04)
2nd trimester	1.00 (0.98–1.02)*	0.99 (0.96–1.01)*	1.01 (0.98–1.03)
3rd trimester	1.01 (0.99–1.03)*	0.98 (0.95–1.02)	0.98 (0.95–1.02)
Whole pregnancy	1.00 (0.98–1.02)	0.99 (0.96–1.02)*	1.01 (0.98–1.04)
O_3 (10 ppb)			
1st trimester	1.01 (0.96–1.06)	1.01 (0.94–1.09)*	0.99 (0.92–1.06)
2nd trimester	0.96 (0.91–1.01)	1.01 (0.94–1.08)*	0.92 (0.85–0.98)*
3rd trimester	0.99 (0.93–1.04)*	0.98 (0.90–1.08)*	0.98 (0.90–1.08)*
Whole pregnancy	0.97 (0.91–1.04)	1.01 (0.92–1.11)*	0.94 (0.85–1.03)*

Abbreviations: CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; SO_2, sulfur dioxide.
[a]Logistic regression analysis adjusting for sex, maternal age, gestational age, municipal-level socieoeconomic status (SES), season of conception, and year of birth. [b]Logistic regression analysis adjusting for sex, maternal age, municipal-level SES, season of conception, and year of birth. *Point estimates were similar with those from the original analyses, but some confidence intervals were wider.

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DDT Paradox

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Bouwman et al. (2011) characterized anti-DDT, centrist-DDT and pro-DDT positions, and stated that they "could find no current outright anti-DDT activities." This conclusion is false and misleading.

Several activist groups currently promote an anti-DDT agenda, routinely hyping supposed human health and environmental harm from DDT and ignoring studies that find no association between DDT and such harm. For instance, the description of Biovision's "Stop DDT" project states that "Biovision is engaged to achieve a worldwide ban on DDT" (Biovision 2011). Such a statement could be ignored if it were not for the fact that Hans Herren, president of Biovision, was a member of the Stockholm Convention's DDT Expert Group, as were two of the authors of Bouwman et al. (2011)—Bouwman and van den Berg. Furthermore, Bouwman et al. ignored the Secretariat of the Stockholm Convention's promotion of an arbitrary deadline for cessation of DDT production by 2020 (United Nations Environment Programme 2007). The Secretariat's promotion of this deadline undermines use and production of DDT and is *ultra vires,* because the convention excludes any deadline.

In identifying the "pro-DDT" faction, Bouwman et al. (2011) attempted to characterize it as a minority view while ignoring national malaria control programs and ministers of health who repeatedly proclaim the importance of DDT for disease control programs in countries with high incidence of malaria. Indeed, the Southern African Development Community (SADC) Ministers of Health agreed at their November 2010 meeting that DDT was still required (SADC 2011). In addition, at the recent fifth meeting of the Conference of Parties to the Stockholm Convention, Namibia and the

SADC announced their intention to produce DDT locally (SADC 2011). Furthermore, the 35 heads of state and government who are members of the African Leaders Malaria Alliance (ALMA) recently endorsed use of DDT in indoor residual spraying (IRS) (ALMA 2010). Such organized actions by affected countries bespeak broad recognition of scientific issues and continuing need for DDT in malaria control programs. Those actions expose the misrepresentations of those who contend support for DDT is limited to a small number of extremists.

Bouwman et al. (2011) argued that "evidence of adverse health effects due to DDT … is mounting" and therefore DDT should be accompanied by information on the potential side effects, just as with prescription medicine. We believe that the interpretation of the mounting evidence is itself a minority view and that their argument is false.

The World Health Organization's (WHO) review of human health aspects of DDT use in IRS concluded that "for households where IRS is undertaken, there was a wide range of DDT and DDE serum levels between studies. Generally, these levels are below potential levels of concern for populations" (WHO 2011). None of the thousands of studies that have been conducted regarding possible human health effects of DDT satisfy even the most basic epidemiological criteria to prove a cause-and-effect relationship. In their commentary, Bouwman et al. (2011) confused a large number of studies that uniformly fail the criterion of consistency in demonstrating that DDT causes actual harm, with isolated studies revealing some statistical association or correlation as a suggestion of harm. It is on this basis that the authors argued for precaution in the use of DDT. In contrast, we argue that precaution should govern Bouwman et al.'s aggressive anti-DDT campaigning and not precaution in the use of DDT to prevent disease and save lives. The growing number of studies is not proof or evidence that DDT causes harm, but it is evidence of growing funding for research on this topic.

Bouwman et al. (2011) argued that households should be informed about unproven and speculative risks from DDT. Their argument must be rejected as the worst form of scaremongering because it will result in growing risk of disease and death from malaria while providing no proven health benefit. Ignoring proven and catastrophic health decrements from malaria infections while warning of theoretical concerns about DDT exposures is a function of ideology. Such precautionary messaging is not good public health policy or sound science.

R.T. is the director of Africa Fighting Malaria (AFM), a policy and advocacy group, and both R.T. and D.R. serve on the AFM board. The organization has offices in South Africa and the United States and conducts critical analysis of malaria control programs and funding agencies and strives to build more transparent, accountable, and effective malaria control programs. AFM has worked to defend the decisions of malaria control programs to use DDT and to argue for a sound, scientific assessment of the chemical. AFM does not now, or in the past, accept funds from the insecticides industry.

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DDT Paradox: Bouwman et al. Respond

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In our commentary (Bouwman et al. 2011), we presented our centrist point of view on DDT, briefly, that despite DDT's known protective effects against malaria, there is a need to eventually eliminate its use due, in part, to growing concerns about DDT's human health impacts. How this can be misrepresented as anti-DDT by Tren and Roberts is simply astounding.

The reference to "isolated studies" on health aspects of DDT by Tren and Roberts has no basis. Of the 22 epidemiological studies from 2009 that we cited, 12 showed that DDT was significantly associated with some condition. We also notice that their "thousands of studies" is not substantiated by references. The evidence we presented is consistent with that of Eskenazi et al. (2009) and justifies our recommendation to invoke precaution.

Tren and Roberts refer to the recent Convention of the Parties of the Stockholm Convention (COP-SC) and the DDT Expert Group's report to the COP-SC (UNEP 2011b). The report stated that

> In certain settings, there is a continued need for DDT for malaria vector control, until locally appropriate and cost-effective alternatives are deployed for a sustainable transition away from DDT. (UNEP 2011b)

Moreover, the COP-SC report (UNEP 2011a) stated that "there was broad support for the recommendation by the DDT expert group that DDT was needed in some countries for disease vector control." It is simply impossible to construe this statement as "anti-DDT."

Most, if not all, of the actions considered by Tren and Roberts as "anti-DDT" can be aligned with a centrist point of view, because most countries involved are Parties to the SC. The COP-SC final report (UNEP 2011a) stated that "there was broad agreement regarding the need to combat malaria and to reduce and eventually eliminate the production and use of DDT."

Regarding the World Health Organization (WHO) assessment of DDT (WHO 2011) quoted in their letter, Tren and Roberts fail to add the qualification included in the same paragraph, namely,

> In some areas, the exposures in treated residences have been higher than potential levels of concern. Efforts are needed to implement best practices to protect residents in treated households from exposures arising from IRS [indoor residual spray]. Of particular concern would be women of childbearing age who live in DDT IRS-treated dwellings and transfer of DDT and DDE to the fetus in pregnancy and to the infant via lactation.

This is what we concluded in our commentary (Bouwman et al. 2011).

WHO procedures recommend the removal of furniture and food from houses to be sprayed, as well as a no-entry period (Najera and Zaim 2002). This implies an explanatory obligation toward the households why this has to be done. Nowhere in our commentary did we actually argue "that households should be informed about" the possible effects of DDT, as purported by Tren and Roberts. We maintain however, that the use of any insecticide in IRS raises ethical issues. This requires further investigation; the implications for IRS are yet unknown.

We defined our position as centrist because we acknowledge the role of DDT in malaria vector control as well as the urgency to move away from DDT once suitable, safe, and sustainable alternatives are in place.